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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,611	05/20/2002	Corinne Elizabeth Augelli-Szafran	5941-01-DRK	3758

7590 08/05/2003

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: ~~08/05/2003~~ 10/29/03

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,611	AUGELLI-SZAFRAN ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *28-31* is/are withdrawn from consideration.

5)☒ Claim(s) *19-21,23-27, 32-35, and 37-41* is/are allowed.

6)☒ Claim(s) *1-9,42 and 43* is/are rejected.

7)☒ Claim(s) *10-18,22 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-43 are pending.

Restriction/Election

2. Applicant's election with traverse of Group II, Claims 1-27 and 32-43 in Paper No. 8 is acknowledged. The traversal is on the ground that the PCT application when subjected to International Preliminary Examination Report (prepared under Article 36 and Rule 70), did not identify any lack of unity inventions amongst similar claims. This is not found persuasive because the United Sates Patent and Trademark Office is *not* bound by the lack of unity determination by another International Searching Authority. MPEP 1875 states that whether or not the question of unity of invention has been raised by the International Searching Authority, it may be considered by the examiner when serving as an authorized officer of the International Preliminary Examining Authority. Thus, the Examiner is *not* bound by any previous determination made. In addition, 37 C.F.R. 1.484 indicates that the international preliminary examination is a non-binding opinion. Finally, 37 C.F.R. 1.499 states that, if the Examiner finds that a national stage application lacks unity of invention under 37 C.F.R. 1.475, the Examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted. Thus, the determination of lack of unity is proper under the PCT treaty.

The traversal is also on the ground(s) that the restriction requirement is inadequate under USPTO regulations and that there is no section of the MPEP that

permits the imposition of a restriction requirement based on different meaning of a radical within a single generic chemical formula. The examiner disagrees with applicants. Restriction is proper within a claim or within a single generic chemical formula. According to 37 CFR §1.475 (e) that states "The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim." The claimed inventions are distinct one from the other. One skilled in the art would not consider a pyridyl group (heterocyclic) as equivalent to a phenyl group (non-heterocyclic).

In regard to traverse about the election of species, it was done merely to initiate a search or to transfer the case within USPTO. Since the examiner retained the case and also examined the entire invention of Group II, the traverse is moot.

Furthermore, the coexamination of each of the additional groups would require search of subclasses unnecessary for the examination of the elected claims. For example, the search for the invention of Group I would include search of class 546, the search for the invention of Group III-IV would include search of class 424 and subclasses 1.11, 1.65, and 9.1. Therefore, coexamination of each of these additional inventions would require a serious additional burden of search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 28-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Objections

3. Claims 10-17, 22 and 36 are objected because they are drawn to multiple inventions. The claims are examined only to the extent that they read on the elected invention (Group II). Cancellation of the non-elected subject matter is recommended in response to this Office Action. This can be done by deleting A = **N** and limit the invention to A = **C**. Note that the last two species in claim 22 (page 123) also have to be deleted, since they don't belong to any of the inventions.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claims 1-9, there has been recited a method of treating Alzheimer's disease, but the specification is not enabled for such a scope.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claims 1-9 are directed to a method of treatment for Alzheimer's disease comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I.

Scope of Compounds - The scope of the compounds is broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of R^1- R^6, R^a, and n.

(2). Direction of Guidance: The amount of direction or guidance is minimal. No data on any specific compound is given. No dosage guidance is provided.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to the compounds of Formula I are in use for the treatment of Alzheimer's disease.

(4). Working Examples: The working example includes the test of 157 compounds for the inhibition of β-Amyloid protein aggregation. Said compounds exhibited inhibitory activities (IC_{50}) ranging from 0.1 μM to greater than 100 μM (more than 1000 fold). According that Table on pages 98-102, some compounds have failed to inhibit β-Amyloid peptide production (e.g. Compounds 52-53 and 83-84). In addition, there is no way to convert the data provided in Table 1 into specific useful knowledge.

(5). Nature of the Invention and Predictability: The invention is directed to inhibiting β-Amyloid protein aggregation in order to treat Alzheimer's disease. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(6). The Relative Skill of Those in the Art: Applicants claim a method of treatment for AD, this is a very hard to treat disease. The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds which are

Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon®, and Reminyl®) a property these compounds are not disclosed to have.

(7). The Quantity of Experimentation Necessary: Immense, especially in view of point 6, since the inhibition of β-Amyloid peptide production for the treatment of AD has never been accomplished. Thus, no guidance from the success of others is available from this experimentation.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Ocain et al (U.S. Pat. No. 5,739,169). Said reference teaches the generic synthesis of benzoic acid derivatives that has the following core structure:

Phenyl-phenyl-NH-benzoic acid.

Specifically, said reference teaches the following compounds:

a. 2-(4'-amino-3,3'-dimethoxy-biphenyl-4ylamino)-benzoic acid (see Example 1, column 6),

b. 2-(4'- bromo-3,3'-dimethoxy-biphenyl-4ylamino)-benzoic acid (see Example 5, column 8),

c. 2-(3,3'dimethoxy-biphenyl-4ylamino)-benzoic acid (see Example 6, column 8),

d. 2-(4'-nitro-3,3'-dimethoxy-biphenyl-4ylamino)-benzoic acid (see Example 7, column 9),

e. first, third and fourth compounds of Example 9 (columns 9-10) and

f. see also compounds of Examples 10-14 (columns 9-12).

Said compounds listed in a-f are the same as applicants when applicant's Formula I has the following substituents:

R^a = H; n = 0; R^8 = tetrazolyl, COOH; R^1, R^2 or R^7 = H, NH_2, NO_2, OCH_3, Br; R^3, R^4 = H, OCH_3 and R^5= R^6 = H.

Since said compounds are the same as applicants, a 102(b) rejection is proper.

6. Claim 42 is rejected under 35 U.S.C. 102(b) as being anticipated by Bowman et al. {Journal of the Chemical Society, Perkin Transactions 1: Organic and Bioorganic Chemistry (1972-1999) (1973), (1), 1-4}. The cited reference on page 2 (see Ring B (iii) compounds 11 and 13) teaches the synthesis of 2-[[2,6-dimethyl-3-(phenylmethyl)phenyl]amino] Benzoic acid and 2-[[2,6-dimethyl-3-[(methylphenyl)methyl]phenyl]amino] Benzoic acid. Since said compounds are the same as applicants, a 102(b) rejection is proper.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Mukund J. Shah

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mukund J. Shah
Supervisory Patent Examiner
Art Unit 1624

KH
October 24, 2003